PRELIMINARY: IDS FEE

Initially, Applicants note that an Information Disclosure Statement was filed May 3, 2004, after the mailing date of the Final Office Action. Applicants inadvertently indicated that no fee was believed to be due. Applicants now realize that a fee of **$180** is believed to be due for the submission of the IDS and request that the proper fee be charged to Winston & Strawn LLP Deposit Account No. 50-1814, so that the IDS may be properly considered and made of record by the Examiner.

REMARKS

Claims 1-5, 7, 10, 15-16, 19-20, and 23-34 are pending in this application for the Examiner's review and consideration. Before responding to the rejection, Applicants will present a summary of the claims of the present invention.

Claims 1-5 and 15-16 of the present invention relate to a bioadhesive, controlled, sustained release progressive hydration pharmaceutical composition in the form of a tablet. The tablet comprises (1) an active ingredient of sex hormones; (2) a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer; and (3) a water soluble polymer. The composition is formulated in a dry state to progressively hydrate and deliver the tablet to the mucous membrane and the active ingredient into the bloodstream.

Claims 7 and 29-30 relate to a method of delivering a sex hormone to a mammal comprising administering a progressive hydration bioadhesive composition to the mucosal surface of the mammal. The composition is a dry tablet that includes (1) the sex hormone; (2) a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer; and (3) a water soluble polymer.

Claims 10 and 19-20 relate to a method of delivering testosterone to a mammal comprising administering a progressive hydration bioadhesive composition to the mucosal surface of the mammal. The composition is a dry tablet that includes (1) testosterone; (2) a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer; and (3) a water soluble polymer.

Claims 23-28 relate to a bioadhesive, progressive hydration pharmaceutical composition comprising (1) testosterone; (2) a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer; and (3) a water soluble polymer. The composition is formulated to progressively hydrate and deliver the testosterone to the bloodstream of the mammal through the mucosal surface.

Claims 31-32 relate to a bioadhesive, progressive hydration pharmaceutical composition comprising (1) testosterone; (2) polycarbophil; and (3) a water soluble polymer. The composition is formulated to progressively hydrate and deliver the testosterone to the bloodstream of the mammal through the mucosal surface.

Claims 33-34 relate to a method of administering testosterone to a mammal comprising delivering the testosterone by a progressive hydration bioadhesive composition through a mucosal surface. The composition includes (1) testosterone; (2) polycarbophil; and (3) a water soluble polymer.

Claims 1-5, 7, 10, 15-16, 19-20, and 23-34 were rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,063,404 to Timpe et al. ("Timpe") "for the reasons on record." Applicants respectfully traverse the rejection.

Timpe discloses a bioadhesive tablet containing at least one bioadhesive adjuvant and at least one lubricant. The surface of the tablet includes certain depressions that permit an active ingredient to be efficiently delivered to the mucosa of a patient. Timpe seeks to improve the passage of active ingredients through the mucosa (*See, e.g.*, column 2, lines 45-49). The active ingredients are made available for resorption across an extensive tissue area of the target organ (*see, e.g.*, column 2, lines 60-65), and the tablet is to adhere to as large a contact area as possible with the mucosa (*See, e.g.*, column 4, lines 18-22).

> The bioadhesive adjuvant should preferably be a substance that develops adhesion when coming into contact with the mucosa, such as a cellulose, a cellulose derivative, a carboxyvinyl polymer, a derivative of a carboxyvinyl polymer, a lectin or natural material or mixtures of said substances. (Column 3, lines 3-8).

(*See also* column 3, lines 37-43).

An obviousness rejection requires: (1) a disclosure or suggestion in the reference of each element of the claimed invention; (2) a motivation to modify the reference that would result in the claimed invention; and (3) a reasonable expectation of successfully making such a modification of the references. In the present application, none of these requirements has been satisfied, such that no *prima facie* case of obviousness has been established.

As detailed above, the claims of the present invention relate to compositions and methods for delivery of a sex hormone (in some claims specifically testosterone) to a mammal through the mucous membrane. The composition is formulated to progressively hydrate and release the active ingredient over an extended period of time. The bioadhesion and sustained release mechanism of the invention is accomplished by the particular polymer

combination claimed, *i.e.*, the bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer and the water soluble polymer.

Prior art tablets attempted to use only a water soluble polymer. These tablets would only adhere to the wall of a body cavity for a short period of time, less than six hours (*See, e.g.*, Specification, page 2, lines 23-29). These tablets are easily dislodged from the wall of the body cavity and if administered buccally, may be asphyxiated (*See, e.g.*, Specification, page 2, lines 29-32). Additionally, these tablets become hydrated relatively quickly, which prematurely exposes the active ingredient to degradation by moisture or enzymes (*See, e.g.*, Specification, page 2, line 32 to page 3, line 4).

Other prior art tablets have used insoluble polymers. These tablets attach for prolonged periods of time, but do not soften properly for comfort and imperceptibility during use. These compositions have also presented safety problems by asphyxiation (*See, e.g.*, Specification, page 3, lines 5-14).

Therefore, the present invention uses a combination of a water soluble polymer and a water insoluble, water-swellable cross-linked polycarboxylic polymer. The polycarboxylic polymer provides good bioadhesion to offset this shortcoming of the water soluble polymer. The water soluble polymer permits the tablet to soften for satisfactory use. It has been found that this formulation provides bioadhesion and extended release for more than 12 hours and even more than 24 hours (*See, e.g.*, Specification, Charts 1-4 and accompanying text).

The composition is formulated in a dry state to protect the active ingredient from moisture and the environment of the mucosal surface. Such surfaces may have varying pH and enzymes that may prematurely break down the active ingredient. The composition progressively hydrates over a period of time, such as 12 to 24 hours, to permit the active ingredient to be released over that time and prevent premature degradation (*See, e.g.*, Specification, page 13, lines 1-23).

The rejection based on Timpe does not meet the first requirement to establish a *prima facie* case of obviousness, as Timpe does not disclose or suggest each element of the claims. Timpe does not disclose or suggest an extended release formulation, a tablet that includes both a water soluble polymer, and a water insoluble, water-swellable cross-linked polycarboxylic polymer, or a formulation that progressively hydrates.

The Office Action indicates that "[t]he claim mentions no particular polymer combination (amounts/ratios)." Applicant agrees that the claims do not recite an amount of the water soluble and the a water insoluble, water-swellable cross-linked polycarboxylic

polymer. This is precisely because Timpe does not recite this combination of polymers, such that there is no particular reason to limit the claims such. In fact, it is unclear how the claims would be limited to avoid Timpe since Timpe does not provide any such disclosure to avoid.

The Office Action also indicates on page 3 that "Timpe reads on the invention since Timpe also suggests a combination of the same polymers. See column 3 lines 3-9, 37-43." As recited above, these sections of Timpe merely disclose that the bioadhesive adjuvant may be a cellulose, a cellulose derivative, a carboxyvinyl polymer, a derivative of a carboxyvinyl polymer, a lectin or natural material or mixtures of said substances. As can be readily seen, Timpe does not disclose the particular combination of a water soluble polymer and a water insoluble, water-swellable cross-linked polycarboxylic polymer as recited in the present claims. Presumably, the Office Action is relying on the "and mixtures of said substances" language for the proposition that Timpe reads on the presently claimed combination of polymers. On the contrary, Timpe recites a polymer, a carboxyvinyl polymer (or a derivative thereof), but does not teach the use of two polymers. While that polymer may be mixed with, for example cellulose or a lectin, there is simply not any disclosure of mixtures that include more than one polymer in the mixture. Timpe does not disclose any polymers at all in the examples therein. Furthermore, there is absolutely no disclosure or suggestion of the particular polymer combination recited in the present claims, the water soluble polymer with the water insoluble, water swellable cross-lined polycarboxylic polymer. Therefore, Timpe does not disclose or suggest each element of the present claims, as would be required to establish a *prima facie* case of obviousness.

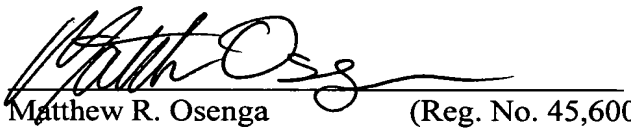
Timpe does not provide any motivation to modify the formulation described therein to achieve the composition of the present invention. Timpe does not indicate how the composition would be modified to provide extended release. Indeed, Timpe teaches an immediate release composition in that the active ingredients are made available for resorption across an extensive tissue area of the target organ (*see, e.g.*, column 2, lines 60-65), and the tablet is to adhere to as large a contact area as possible with the mucosa (*See, e.g.*, column 4, lines 18-22).

Likewise, Timpe uses the depressions recited therein to accomplish its goal of permitting an active ingredient to be efficiently delivered to the mucosa of a patient and does not provide any motivation or suggestion to modify its formulation to include the particular polymer combination recited in the present claims. Timpe is concerned with improving passage of the active ingredient to the mucosa, while the presently claimed invention is concerned with providing extended release in a manner to protect the active ingredient from

the mucosal environment so that it may be released over an extended period of time without premature degradation. Thus, Timpe provides no motivation to modify the composition described therein to achieve the presently claimed invention. Because they are resolving inherently different problems, one of skill in the art would not have reasonably expected to successfully modify the composition described in Timpe to achieve the presently claimed invention. Thus, a *prima facie* case of obviousness has not be established with respect to Timpe. For these reasons, Applicants respectfully submit that rejection of claims 1-5, 7, 10, 15-16, 19-20, and 23-34 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Accordingly, all claims are believed to be in condition for allowance. Should the Examiner not agree, then a personal or telephone interview is respectfully requested to discuss and resolve any remaining issues to allowance of this application.

Respectfully submitted,



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Date

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